2. Amend § 288.7(d)(1) by adding a proviso to read as follows:

* * * * *

(d) For Category A transportation services on and after

(1) Passengers, 7.044 cents per passenger-mile: *Provided,* That a carrier may perform Category A passenger services at a rate per passenger-mile which, when applied to the mileage between specific points in accordance with subparagraph (3) of this paragraph, produces a product fare equal to a published, unrestricted, one-way, passenger tariff fare that is in fact available to the general public for equivalent services, in the event that the Category A rate per passenger-mile, specified above, would result in a higher charge than such published tariff.

(2) * * *

* * * * *

(Secs. 204, 403 and 416 of the Federal Aviation Act of 1958, as amended; 72 Stat. 743, 758 and 771, as amended; (49 U.S.C. 1324, 1373 and 1386).)

By the Civil Aeronautics Board.

PHYLLIS T. KAYLOR,
Secretary.

APPENDIX I—SUMMARY OF SEATING CONFIGURATIONS IN CHARTER AND SCHEDULED SERVICES

Aircraft type	Carrier	Charter service	Scheduled service
B-747	AA	364-424	343
	BN	356	356
	DL	370	370
	NW	369, 375	369
	PA	373, 381, 400, 408 437, 453.	373, 400
	TW	363	363
	UA	342, 374	342
	World	357, 395, 411, 423, 445, 461.	—
L-1011	DL	256, 264	256
	EA	256	261
DC-10-10	AA	240	240
	UA	242, 259	241
DC-30	NA	283	269
	TIA	275, 303, 345, 376.	—
DC-40	NW	236	236

WIDE-BODY AIRCRAFT SEATING DENSITIES PER MANUFACTURER'S SPECIFICATION

Aircraft type	*Number of seats*
B-747100/200B/200C	374-500
DC-10-30/40	250-380
L-1011-1/100/200/250	250-400

[FR Doc. 78-16235 Filed 6-12-78; 8:45 am]

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 10]

[Docket No. 78N-0126]

SEPARATION OF FUNCTIONS AND EX PARTE COMMUNICATIONS

Withdrawal of Proposal and Termination of Rulemaking Proceedings

AGENCY: Food and Drug Administration.

ACTION: Withdrawal of proposal.

SUMMARY: The Commissioner of Food and Drugs is withdrawing a proposal to establish rules concerning separation of functions and ex parte communications. The proposal is being withdrawn because it has been superseded by more recent procedural regulations.

EFFECTIVE DATE: June 13, 1978.

FOR FURTHER INFORMATION CONTACT:

Richard T. Hunt, Compliance Regulations Policy Staff (HFC-10), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3480.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of March 24, 1972 (37 FR 6107), the Commissioner issued a proposal to establish regulations concerning separation of functions and ex parte communications. The proposal was intended, among other things, to more clearly define permissible and impermissible communication among parties to a public hearing and FDA officials, employees, and attorneys.

In the FEDERAL REGISTER of January 25, 1977 (42 FR 4680), the Commissioner adopted new comprehensive administrative practices and procedures that encompassed the issues of separation of function and ex parte communications.

Accordingly, the Commissioner announces that the proposal published in the FEDERAL REGISTER of March 24, 1972 (37 FR 6107) is now superseded and is hereby withdrawn.

This withdrawal is issued under the Federal Food, Drug, and Cosmetic Act (sec. 701, 52 Stat. 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 371)) and under the Administrative Procedure Act (secs. 4,5, 60 Stat. 238, 239 as amended (5 U.S.C. 553, 554)) and under authority delegated to the Commissioner (21 CFR 5.1).

Dated: June 5, 1978.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 78-16089 Filed 6-12-78; 8:45 am]

[1505-01]

[21 CFR Parts 182, 184]

[Docket No. 78N-0015]

INOSITOL

Proposed Affirmation of Gras Status as a Direct Human Food Ingredient

Correction

In FR Doc. 78-13715 appearing at page 22056 in the issue for Tuesday, May 23, 1978, make the following corrections:

(1) On page 22057, in the first column, in the next to last line, "O-B-D-galactopyranosyl myo-inositol" should read "O-β-D-galactopyranosyl myo-inositol."

(2) On page 22058, in the middle column, in § 184.1341(a), in the third line, delete the space between "trans-4," and "6-cyclohexanehexol."

[4110-03]

[21 CFR Parts 182, 184, 186]

[Docket No. 78N-0071]

CARBONATES AND BICARBONATES

Proposed Affirmation of GRAS Status as Direct and Indirect Human Food Ingredients

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This is a proposal to affirm the generally recognized as safe (GRAS) status of calcium carbonate, potassium bicarbonate, potassium carbonate, sodium bicarbonate, sodium carbonate, and sodium sesquicarbonate as direct human food ingredients, and of sodium bicarbonate and sodium carbonate as indirect human food ingredients. The safety of these ingredients has been evaluated under a comprehensive safety review being conducted by the agency. The proposal would list calcium carbonate, potassium bicarbonate, potassium carbonate, sodium bicarbonate, sodium carbonate, and sodium sesquicarbonate as direct food substances affirmed as GRAS, and sodium bicarbonate and sodium carbonate as indirect food substances affirmed as GRAS.

DATE: Comments by August 14, 1978.

ADDRESS: Comments (preferably four copies) to the Hearing Clerk (HFC-20), Food and Drug Administration, room 4-65, 5600 Fishers Lane, Rockville, MD 20857.

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FOR FURTHER INFORMATION CONTACT:

Corbin I. Miles, Bureau of Foods (HFF-335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C Street SW., Washington, D.C. 20204, 202-472-4750.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs has issued several notices and proposals (see the FEDERAL REGISTER of July 26, 1973 (38 Fr 20040)) initiating a comprehensive safety review of human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. Under this review, which is being conducted by the Food and Drug Administration (FDA), the safety of calcium carbonate, potassium bicarbonate, potassium carbonate, sodium bicarbonate, sodium carbonate, and sodium sesquicarbonate has been evaluated. Under § 170.35 (21 CFR 170.35), the Commissioner proposes to affirm the GRAS status of these ingredients. Ammoniuim bicarbonate, ammonium carbonate, and magnesium carbonate will be considered in other proposals on ammonium and magnesium salts, respectively.

Carbonates and bicarbonates are commonly used in foods as neutralizers and leavening agents. These anions occur in body fluids and tissues as the result of normal metabolic processes and are important in the control of acid-base balance. Their salts are usually colorless or white translucent or transparent crystals, flakes, powders, or granules. Except for calcium carbonate, most of the carbonates used in foods are fairly soluble in water. They may decompose in dry and/or moist air with temperature gradients proportionately influencing the rate of degradation.

Calcium carbonate, potassium bicarbonate, potassium carbonate, sodium bicarbonate, sodium carbonate, and sodium sesquicarbonate are listed in §§ 182.1191, 182.1613, 182.1619, 182.1736, 182.1742, and 182.1792 (21 CFR 182.1191, 182.1613, 182.1619, 182.1736, 182.1742, and 182.1792), respectively, as multiple purpose GRAS food substances, under regulations published in the FEDERAL REGISTER of November 20, 1959 (24 FR 9368) and subsequently recodified. Calcium carbonate is also listed in § 182.5191 (21 CFR 182.5191) as a nutrient and dietary supplement, under regulations published in the FEDERAL REGISTER of November 20, 1959 (24 FR 9368), and is prior sanctioned for use as a stabilizer in § 181.29 (21 CFR 181.29). Sodium bicarbonate and sodium carbonate are listed in § 182.70 (21 CFR 182.70) for use in cotton and cotton fabrics used in dry food packaging, under regulations published in the FEDERAL REGISTER of June 10, 1961 (26 FR 5224). Sodium carbonate is also listed in § 182.90 (21 CFR 182.90) for use in paper and paperboard packaging materials, under regulations published in the FEDERAL REGISTER of June 17, 1961 (26 FR 5421).

Certain Federal standards of identity list the use of some bicarbonates and carbonates in food: Calcium carbonate in frozen desserts (Part 135 (21 CFR 135)), cereal flours and related products (Part 137 (21 CFR 137)), and food dressings and flavorings (Part 169 (21 CFR Part 169)); sodium bicarbonate in cereal flours and related products (Part 137), canned vegetables (Part 155 (21 CFR Part 155)), and cacao products (Part 163 (21 CFR Part 163)); sodium carbonate in canned vegetables (Part 155), and cacao products (Part 163); and potassium bicarbonate and potassium carbonate in cacao products (Part 163).

Sodium bicarbonate is cleared by the Meat Inspection Division (MID) of the United States Department of Agriculture, to separate fatty acids and glycerol in rendered fats, and for use as a cooling and retort water treatment agent for prevention of staining exterior surfaces of food cans. Sodium carbonate is cleared by MID to refine rendered fats, to denude mucous membranes from tripe, and as a cooling and retort water treatment agent for prevention of staining exterior surfaces of food cans. The Bureau of Alcohol, Tobacco, and Firearms has cleared calcium carbonate and sodium carbonate under § 240.1051 (27 CFR 240.1051) to reduce excess natural acids in wine. Potassium carbonate and sodium carbonate are regulated as food additives in § 173.310 (21 CFR 173.310) as components of boiler water additives. Calcium carbonate is also regulated as a food additive in § 175.300 (21 CFR 175.300) for use in resinous and polymeric coatings, and in § 177.1600 (21 CFR 177.1600) for use in polyethylene resins, carboxyl modified.

A representative cross-section of food manufacturers was surveyed to determine the specific foods in which carbonates and bicarbonates have been used and the levels of usage. Information from surveys of consumer consumption was obtained and combined with the manufacturing information to obtain an estimate of consumer exposure to these ingredients. The total amounts of these ingredients used by the United States food industry in 1970 were 33 million pounds of calcium carbonate, 37,000 pounds of potassium bicarbonate, 4 million pounds of potassium carbonate, 95 million pounds of sodium bicarbonate and 35 million pounds of sodium carbonate. No food-use data were reported for sodium sesquicarbonate in these surveys. From industry sources, however, it was reported that 712,000 pounds of sodium sesquicarbonate were sold in 1970. The total amount of carbonates and bicarbonates (including ammonium bicarbonate and ammonium carbonate) used in food in 1970 is more than double that used in 1960.

The carbonates and bicarbonates have been the subject of a search of the scientific literature from 1920 to the present. The criteria used in the search were chosen to discover any articles that considered: (1) chemical toxicity; (2) occupational hazards; (3) metabolism; (4) reaction products; (5) degradation products; (6) any reported carcinogenicity, teratogenicity, or mutagenicity; (7) dose response; (8) reproductive effects; (9) histology; (10) embryology; (11) behavioral effects; (12) detection; and (13) processing. A total of 874 abstracts on carbonates was reviewed and 70 particularly pertinent reports from the literature survey have been summarized in a scientific literature review.

The scientific literature review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances (the Select Committee), selected by the Life Sciences Research Offices of the Federation of American Societies for Experimental Biology:

The biochemical role of the bicarbonate salts has been studied for over 50 years. Investigations using radioisotope procedures have educed extensive information concerning their absorption, metabolism, excretion, and control of acid-base balance of the body. The Select Committee has found few reports of experiments expressly designed to determine the oral toxicity, mutagenicity, teratogenicity or carcinogenicity of the various carbonate compounds. Knowledge of specific toxic levels and the effects of long-term feeding on various species of animals is lacking.

Orally administered to an unstated number of rats, potassium carbonate had an LD_{50} of 1.87 g per kg. Potassium bicarbonate caused an 80 percent increase in intercalated cells of the collecting tubules of the kidneys of rats 4.5 hours after intubation of 345 mg.

Ten chicks fed potassium bicarbonate as a 3 percent supplement to a basal diet for up to four weeks showed no signs of illness, although two chicks developed white liver nodules. In other animal studies, 11 lambs fed a concentrated ration supplemented by 2 percent of 1:1 mixture of sodium and potassium bicarbonate for 59 days showed an increase in weight gain, feed consumption and feed efficiency.

Potassium carbonate in *in vitro* microbial assays was not mutagenic in assays with *Saccharomyces cerevisiae*, strain D4 and

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Salmonella typhimurium, strains TA-1535, TA-137, and TA-1538. Tissue homogenates for plate and suspension activation assays were prepared from liver, lungs and testes of mice, rats and monkeys.

Teratologic evaluation of potassium carbonate was performed in mice and rats. The administration of up to 290 mg per kg to pregnant mice and up to 180 mg per kg to pregnant rats for 10 consecutive days (day 6 through day 15 of gestation) had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test group did not differ from the number occurring spontaneously in the shamtreated controls.

The acute oral toxicity of sodium bicarbonate was studied in intubated Wistar SPF rats weighing 100 to 150 g; LD_{50} levels reported were 8.9 g per kg in fed rats, 7.57 g per kg in fasted rats on wire floored cages, and 8.46 g per kg in fasted rats bedded on wood shavings. Dose volume was influential: the LD_{50} was 8.39 g per kg in fed rats receiving 20 to 25 ml per kg, compared to 5.85 g per kg in fed rats receiving 32 ml per kg. In another study using 200 g rats, the LD_{50} levels observed at 20 ml per kg and 50 ml per kg were 5.5±0.6 g per kg and 4.85±0.3 g per kg, respectively. Intubation of 290 to 493 mg of sodium bicarbonate caused an 80 percent increase in intercalated cells of the collecting tubules of the kidneys of rats.

The intraperitoneal injection of 18 Ci of sodium [^{14}C] bicarbonate into CFW mice was followed by assays (after 24 and 48 hours and 1,2,4, and 12 weeks) of blood, spleen, liver, kidneys, lungs, brain, jejunum, muscle, skin, hair, and long bones. More than 90 percent of the total radioactivity injected was lost via the respiratory route in one hour. At 24 hours, most of the radioactivity in the blood was in noncarbonate form. Specific activity in long bones paralleled that in the blood for up to 12 weeks. The radioactivity of the compound injected into a pregnant mouse was fixed in the fetal tissues more rapidly than in the maternal tissues. Variable and transient responses in erythrocyte counts and hemoglobin levels in mice to orally administered sodium bicarbonate were reported.

Rapid absorption was demonstrated in rats after intraperitoneal injection of less than one mg sodium [^{14}C] bicarbonate. Expired radioactivity reached a maximum specific activity within 4 to 10 minutes, and by 13 to 16 minutes the specific activity was reduced by half. In a further study, rats were fasted for 24 hours and given lactate by stomach tube, followed by five intraperitoneal injections of sodium [^{14}C] bicarbonate made at 30 minute intervals. The animals were sacrifices one-half hour later and about 60 percent of the label was accounted for. The livers were removed and the glycogen extracted; 0.3 to 1.1 percent of the administered carbon-11 was present in the glycogen. Urine contained 1.3 percent of the dose and over 50 percent of the dose was accounted for by respiratory [^{14}C] carbon dioxide. The authors calculated that one out of eight carbon atoms present in the glycogen was derived from the bicarbonate carbon. Sodium bicarbonate has been reported to affect citrate metabolism in the kidneys or rats. An intraperitoneal injection of 672 mg per kg into four male rats caused a threefold rise in tissue citrate levels of the kidney and a smaller but significant rise in the citrate levels in the liver.

In man, at plasma bicarbonate levels below 24 mM, virtually all bicarbonate entering the renal tubules is reabsorbed. Above this level the excess bicarbonate is excreted. Oral administration of sodium bicarbonate at one g per kg as a single dose increased sodium excretion and decreased blood chloride concentration and urine chloride excretion. These studies demonstrate that the carbonate and bicarbonate ions enter and are constituents of the normal metabolic pathways of man.

As reported in a preliminary paper, two groups of 22 two-week-old chicks were given water containing 0.6 and 1.2 percent sodium bicarbonate for varying periods of time. Those fed the 1.2 percent level developed lesions of gout (kidneys damaged by accumulation of urate crystals with accumulation of water in these organs and other parts of the viscera) as early as the first day. The kidneys of chicks administered 0.6 percent sodium bicarbonate become pale on the first day but did not develop lesions of gout. An autopsy showed that all chicks, fed the higher level of bicarbonate developed urate crystales in their kidneys by the third or fourth days. Mature cockerels were not injured by feeding the 1.2 percent solution, but 2.4 percent caused clinical signs of gout and death within five days. The investigators inferred that age and severity of lesions were inversely correlated. In another study of poultry, three two-week-old ducklings received 2 percent sodium bicarbonate in their drinking water and died within 3 days; kidney damage was reported.

Intravenous administration of sodium bicarbonate over 7 days for an average total dose of 3.7 g per kg produced no pathological changes in any of 28 rats. The total dose was given in one to seven daily injections, the average being 3.7 injections. The same investigators reported no pathological kidney changes in nine rabbits receiving 2.3 g per kg of sodium bicarbonate intravenously or in four rabbits receiving 6.4 g per kg subcutaneously over a one-week period.

Additional effects on metabolism have been reported in rats and guinea pigs. Intubation of 0.2 to 0.5 g of sodium bicarbonate decreased the amount of liver glycogen in fasted rats within 3 hours. When fed in the diet, it induced increased excretion of β-hydroxybutyric acid and lactic acid in the urine of rats. In the guinea pig, sodium bicarbonate fed for 15 days at a level of 400 mg per kg with ascorbic acid resulted in an increased concentration of ascorbic acid in the adrenals and livers as compared to controls fed ascorbic acid. These observations were apparently not associated with pathologic changes.

The effect of sodium bicarbonate upon gastric secretion was studied in five dogs. Intubation of 75 to 100 mg sodium bicarbonate per kg three times daily increased gastric secretory activity a short time after a meal; later the secretory volume decreased. In a 19 kg dog intravenous injection of 27.4 to 42.5 g of sodium bicarbonate induced alkalosis and caused a decrease in serum calcium, chloride and phosphorus but with a large increase in total base, sodium, and blood bicarbonate. Intravenous addition of sodium chloride did not alter the severity of the alkalosis, and the sodium and total base values were further elevated.

Potassium was retained and ammonia formation decreased in a 25-year-old man who consumed 8.4 g sodium bicarbonate daily (122 mg per kg) for six days. Six adult humans ingested 120 mg per kg of sodium bicarbonate daily for five days. Urine calcium decreased significantly for all six subjects when compared to that of a similar control diet period.

Thirty-three patients with gastric or peptic ulcers were treated via gastric tube with sodium bicarbonate in daily doses of up to 100 g at a constant rate for three weeks. All developed alkalosis as plasma carbon dioxide content rose. Inulin and endogenous creatinine clearances indicated no impairment of renal function. The glomerular filtration rate increased during treatment, but it tended to drop to subnormal and recover to normal levels when therapy stopped. No renal damage was observed. Large amounts of sodium were apparently retained in an expanded extracellular space. Oral administration of large doses (840 mg per kg per day) to an infant for 8 days also caused sodium retention. One 23-year-old patient (54 kg) received a total dose of 3.2 kg sodium bicarbonate over a period of 20 months for treatment of duodenal ulcer, without marked difference in acid-base balance or decrease in urea clearance and with no change in red and white blood cell counts or hemoglobin values.

The effect of oral and intravenous administration of sodium bicarbonate to dogs was studied. One kidney was surgically removed from each dog for comparison of pre- and post-treatment morphology. Nine dogs received gradually increased doses from 5 to 60 g sodium bicarbonate (up to 10 g per kg) per day. Five of these dogs received oral doses for 30 to 114 days. The remaining four dogs received oral doses of sodium bicarbonate daily and intravenous injection each week for a period of 125 to 261 days. Two dogs in the oral dose group survived; the rest died in acute alkalosis. Renal lesions of toxicity were hyperemia, edema and protein precipitation in the tubules. The dogs receiving the intravenous supplement had the greatest renal damage.

In humans, sodium bicarbonate temporarily decreases protease and amylase activity when introduced directly into the jejunum in isotonic solution. Cardiac and respiratory rate increases associated with hard exercise were more pronounced under the influence of sodium bicarbonate fed to adult men as a single dose (100 mg per kg). Marked diuresis occurred during fatigue. Decreased plasma levels and decreased excretion of ascorbic acid in the urine were observed during a two-week study when 15 g of sodium bicarbonate was fed daily to two female subjects on a diet containing 67 mg of ascorbic acid. Drug interactions reported included an increased absorption rate of sulfadiazine when taken with sodium bicarbonate on an empty stomach but sodium bicarbonate apparently delayed absorption of sulfadiazine if given after a meal.

Sodium bicarbonate was not mutagenic in *in vitro* assays with *Salmonella* or *Saccharomyces*. Sodium bicarbonate and sodium carbonate were not teratogenic in mice or rats. Sodium carbonate was neither toxic nor teratogenic in the chick embryo at levels up to 200 mg per kg.

Studies of metabolism and excretion have included intraperitoneal implantation of 0.40 mCi of calcium [^{14}C] carbonate as a pellet in a male rat. About 72 percent of the radioactivity was excreted as respiratory carbon dioxide between 2 and 142 hours after implantation (most after 69 hours). About 30 percent of the dose was recovered in unabsorbed pellet. Urinary radioactivity accounted for 0.27 percent and fecal radioactivity for about 0.07 percent of the dose; 1 percent of the absorbed dose was retained

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by the tissues. Significant amounts of radioactivity were incorporated into the inorganic fraction of bone and into bone protein, dentin and enamel, as well as in fatty acids, glycerol, hemin, red cell protein, plasma protein, liver and muscle glycogen, muscle protein and the proteins of the testes, thoracic and abdominal viscera; in the kidney, the highest concentration was in the cortex. The same investigators distributed the compound over the peritoneal viscera of a male rat and collected exhaled air. The largest amount of radioactivity in respiratory carbon dioxide was present on the 7th and 8th days; none was detected on the 22nd day.

Calcium [^{14}C] carbonate injected into a rat produced a higher specific activity in the saturated fatty acids than in the unsaturated fatty acids. Similar results were obtained with sodium [^{14}C] carbonate. The carbon-14 content of the carboxyl carbon atoms was twice as high as the average for all fatty acid carbon atoms. Five rats were fed [^{45}C] calcium carbonate for three days at 3 g per kg of feed (0.3 g per kg body weight). All rats remained healthy; calcium-45 was deposited in the femur, demonstrating the availability of calcium in the carbonate form.

In humans it has been reported that calcium carbonate taken orally in single doses from 16 to 200 mg per kg caused a transient rise in blood serum calcium. After 40 g (0.66 g per kg) calcium carbonate was fed daily for 4 days to three adult humans with peptic ulcers, a large reduction of urinary potassium was observed.

Addition of calcium carbonate to the basal diet at levels of 1 and 3 percent resulted in lower tissue iron values in anemic rats; this was interpreted as a disturbance in the normal concentration of inorganic ions in the principal absorptive portions of the digestive tract. Other investigators have shown that low intake of calcium and a high intake of phosphorus can cause impaired iron utilization with anemia. Under some circumstances either calcium salts or phosphate salts may improve iron absorption, while an excess of either may inhibit iron absorption. Calcium carbonate at 7.26 g per pound of flour in an 80 percent bread diet for 10 weeks in anemic rats (about 0.3 g $CaCO_3$ daily per kg body weight) decreased food consumption and decreased weight gain. Even though the treated diet contained supplemental iron, the iron content of the liver decreased and hemoglobin regeneration was retarded; heart weights increased. It was postulated that the calcium saturated the alimentary mucosal cells, presenting a block to the absorption of iron. The calcium:phosphorus ratio of the experimental diet was about 5:1.

Feeding a cariogenic ration consisting largely of coarsely ground corn supplemented with 3 percent calcium carbonate and 2 to 4 I.U. vitamin D for about four months to three groups of weanling rats resulted in marked reduction of weight gain but had no effect on dental caries incidence.

In humans, the oral administration of calcium carbonate to 28 peptic ulcer patients at a level of 500 mg per kg per day, divided into hourly doses during waking hours for three weeks, resulted in six patients developing hypercalcemia (five within 72 hours) with nausea, vomiting, anorexia, weakness, lethargy, headache, and dizziness. Blood urea nitrogen values increased significantly. After withdrawal of calcium carbonate the serum calcium values returned to normal.

Calcium retention increased 86.3 percent, and urinary calcium output also increased, when a basal diet providing 1 g calcium daily was supplemented with 2.5 g calcium carbonate and fed to 10 men for 10 days. This provided calcium carbonate at 40 mg per kg and a daily calcium intake of 2 g.

Female Swiss mice were bred after one week on diets which were supplemented by 0.5, 1.0, and 2.0 percent of calcium carbonate. First and second litters were studied. The highest levels of calcium carbonate gave a calcium carbonate intake of about 3 g per kg body weight and a calcium:phosphorus ratio of 2.3:1. This diet significantly lowered the number and total weight of the weanling mice and increased the number and proportion of deaths as compared to a control diet. The control diet provided 0.34 percent calcium and a calcium:phosphorus ratio of 0.70:1. The diet having the highest calcium content caused hypertrophy of the heart and a tendency toward decrease in thymus weight in the weanling rats. These changes were prevented by supplementing the maternal diets with iron. It has been pointed out in another report by the Select Committee that an excess of dietary calcium may precipitate a deficiency of zinc and perhaps certain other trace inorganic elements.

No specific biological information on sodium sesquicarbonate is available to the Select Committee.

All of the available safety information on bicarbonates and carbonates has been carefully evaluated by qualified scientists of the Select Committee. It is the opinion of the Select Committee that:

* * * [It] is not aware of any long-term experimental studies on chronic administration of any of the carbonate salts. The results of acute toxicity and short-term feeding experiments are not readily extrapolated in determining toxic levels for carbonate salts consumed by humans. Treatment of gastric or peptic ulcers in patients with large amounts of carbonate salts in various forms has been utilized for many years and only rarely have deleterious results of changes of acid-base balance been reported. When the human respiratory and renal functions are normal, the mechanisms for disposing of bicarbonate intake in large amounts through excretion appear to be highly efficient.

Studies of mice suggest that large intakes of calcium carbonate may interfere with reproductive performance. Such effects could be indirectly attributable to certain trace nutrient deficiencies. Comparable intake levels of calcium may occur when calcium carbonate is used for therapeutic purposes but the amounts added to foods in normal manufacturing processes are not high enough to be harmful. While the Select Committee is not aware of any studies on sodium sesquicarbonate *per se*, reasoned judgment suggests its biochemical conversion and metabolism would be similar to that of sodium carbonate and bicarbonate.

The Select Committee concludes that there is no evidence in the available information on calcium carbonate, potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, or sodium sesquicarbonate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when used at levels that are now current or that might reasonably be expected in the future. Based upon his own evaluation of available information on these carbonates and bicarbonates, the Commissioner concurs with this conclusion. The Commissioner therefore maintains that no change in the current GRAS status of these ingredients is justified. Ammonium bicarbonate, ammonium carbonate, and magnesium carbonate will be considered in other proposals on ammonium and magnesium salts, respectively.

Copies of the scientific literature review on the carbonates, mutagenic evaluations of potassium carbonate and sodium bicarbonate, teratogenic evaluations of potassium carbonate, sodium bicarbonate, and sodium carbonate, and the report of the Select Committee are available for review at the office of the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be purchased from the National Technical Information Service, 5285 Port Royal Road, Springfield, Va. 22161, as follows:

Title	Ordering No.	Price code	Price [1]
Carbonates (scientific literature review	PB-221-231	A07	$7.25
Potassium carbonate (mutagenic evaluation)	PB-245-591/AS	A03	4.50
Sodium bicarbonate (mutagenic evaluation)	PB-245-436/AS	A03	4.50
Potassium carbonate (teratogenic evaluation)	PB-245-522/AS	A03	4.50
Sodium bicarbonate (teratogenic evaluation)	PB-234-871/AS	A03	4.50
Sodium carbonate (teratogenic evaluation)	PB-234-868/AS	A03	4.50
Carbonates and bicarbonates (Select Committee report).	PB-254-535/AS	A03	4.50

[1] Price subject to change.

This proposed action does not affect the present use of bicarbonate and carbonate salts for pet food.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes to amend Parts 182, 184, and 186 as follows:

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PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

§ 182.70 [Amended]

1. In § 182.70 *Substances migrating from cotton and cotton fabrics used in dry food packaging* by deleting the entries for "Sodium bicarbonate" and "Sodium carbonate."

§ 182.90 [Amended]

2. In § 182.90 *Substances migrating to food from paper and paperboard products* by deleting the entry for "Sodium carbonate."

§§ 182.1191, 182.1613, 182.1619, 182.1736, 182.1742, 182.1792, and 182.5191 [Deleted]

3. By deleting § 182.1191 *Calcium carbonate*, § 182.1613 *Potassium bicarbonate*, § 182.1619 *Potassium carbonate*, § 182.1736 *Sodium bicarbonate*, § 182.1742 *Sodium carbonate*, § 182.1792 *Sodium sesquicarbonate*, § 182.5191 *Calcium carbonate*.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

4. In Part 184 by adding new §§ 184.1191, 184.1613, 184.1619, 184.1763, 184.1742, and 184.1792 to read as follows:

§ 184.1191 Calcium carbonate.

(a) Calcium carbonate ($CaCO_3$, CAS Reg. No. 471-34-1) is prepared by three common methods of manufacture:

(1) As a byproduct in the "Lime soda process";

(2) By replacement of carbon dioxide in the "Carbonation process"; or

(3) By precipitation of calcium carbonate from calcium chloride in the "Calcium chloride process."

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed (1972), as amended by the first supplement.[1]

(c) The ingredient is used in food as an anticaking and free-flow agent as defined in § 170.3(o)(1) of this chapter, dough strengthener as defined in § 170.3(o)(6) of this chapter, firming agent as defined in § 170.3(o)(10) of this chapter, formulation aid as defined in § 170.3(o)(14) of this chapter, leavening agent as defined in § 170.3(o)(17) of this chapter, lubricant and release agent as defined in § 170.3(o)(18) of this chapter, nutrient supplement as defined in § 170.3(o)(20) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, processing aid as defined in § 170.3(o)(24) of this chapter, stabilizer and thickener as defined in § 170.3(o)(28) of this chapter, and synergist as defined in § 170.3(o)(31) of this chapter.

(d) The ingredient is used in food and infant formulas, in accordance with § 184.1(b)(1), at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.5 percent in baked goods as defined in § 170.3(n)(1) of this chapter, 0.02 percent in nonalcoholic beverages as defined in § 170.3(n)(3) of this chapter, 1.3 percent in breakfast cereals as defined in § 170.3(n)(4) of this chapter, 14 percent in chewing gum as defined in § 170.3(n)(6) of this chapter, 7.5 percent in confections and frostings as defined in § 170.3(n)(9) of this chapter, 0.9 percent in gelatins, puddings, and fillings as defined in § 170.3(n)(22) of this chapter, 1.2 percent in reconstituted vegetables as defined in § 170.3(n)(33) of this chapter, 1.4 percent in soft candy as defined in § 170.3(n)(38) of this chapter, 2.5 percent in sweet sauces, toppings, and syrups as defined in § 170.3(n)(43) of this chapter, 1.4 percent in infant formulas, and 0.3 percent or less in all other food categories.

§ 184.1613 Potassium bicarbonate.

(a) Potassium bicarbonate ($KHCO_3$, CAS Reg. No. 298-14-6) is made by treating a solution of potassium carbonate with carbon dioxide.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used as a formulation aid as defined in § 170.3(o)(14) of this chapter, nutrient supplement as defined in § 170.3(o)(20) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, and processing aid as defined in § 170.3(o)(24) of this chapter.

(d) The ingredient is used in food and infant formulas, in accordance with § 184.1(b)(1) at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 3 percent in confections and frostings as defined in § 170.3(n)(9) of this chapter, and 0.02 percent in infant formulas.

§ 184.1619 Potassium carbonate.

(a) Potassium carbonate (K_2CO_3, CAS Reg. No. 584-08-7) is produced by the electrolysis of potassium chloride followed by exposing the resultant potassium to carbon dioxide.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used in food as a flavoring agent and adjuvant as defined in § 170.3(o)(12) of this chapter, nutrient supplement as defined in § 170.3(o)(20) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, and processing aid as defined in § 170.3(o)(24) of this chapter.

(d) The ingredient is used in food, in accordance with § 184.1(b)(1), at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.5 percent in baked goods as defined in § 170.3(n)(1) of this chapter, 0.01 percent in nonalcoholic beverages as defined in § 170.3(n)(3) of this chapter, 3 percent in confections and frostings as defined in § 170.3(n)(9) of this chapter, 0.2 percent in dairy product analogs as defined in § 170.3(n)(10) of this chapter, and in soft candy as defined in § 170.3(n)(38) of this chapter, and 0.09 percent in sweet sauces as defined in § 170.3(n)(43) of this chapter.

§ 184.1736 Sodium bicarbonate.

(a) Sodium bicarbonate ($NaHCO_3$, CAS Reg. No. 144-55-8) is prepared by dissolving sodium carbonate and treating the solution with carbon dioxide. As carbon dioxide is absorbed a suspension of sodium bicarbonate forms. The slurry is filtered, forming a cake which is washed and dried.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used in food as a curing and pickling agent as defined in § 170.3(o)(5) of this chapter, dough strengthener as defined in § 170.3(o)(6) of this chapter, flavor enhancer as defined in § 170.3(o)(11) of this chapter, flavoring agent and adjuvant as defined in § 170.3(o)(12) of this chapter, leavening agent as defined in § 170.3(o)(17) of this chapter, nutrient supplement as defined in § 170.3(o)(20) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, processing aid as defined in § 170.3(o)(24) of this chapter, propellant and aerating agent as defined in § 170.3(o)(25) of this chapter, stabilizer and thickener as defined in § 170.3(o)(28) of this chapter, surface-active agent as defined in § 170.3(o)(29) of this chapter, and texturizer as defined in § 170.3(o)(32) of this chapter.

(d) The ingredient is used in food and infant food, in accordance with § 184.1(b)(1), at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 6 percent in baked goods as defined in § 170.3(n)(1) of this chapter, 5.6 percent in nonalcoholic beverages as defined in § 170.3(n)(3) of this chapter, 0.07 percent in dairy product analogs as defined in § 170.3(n)(10) of this chapter, 1.3 percent in grain products and pastas as defined in § 170.3(n)(23) of this chapter, 0.8 percent in hard candy and cough drops as defined in § 170.3(n)(25) of this chapter, 2.9 percent in processed fruit and fruit juices

[1] Copies may be obtained from: National Academy of Sciences, 2101 Constitution Avenue NW., Washington, D.C. 20037.

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as defined in § 170.3(n)(35) of this chapter, 1.8 percent in soft candy as defined in § 170.3(n)(38) of this chapter, 0.8 percent in infant baked goods, 0.005 percent in infant formulas, and 0.6 percent or less in all other food categories.

§ 184.1742 Sodium carbonate.

(a) Sodium carbonate (Na_2CO_3, CAS Reg. No. 497-19-8) is derived either from purified trona ore that has been calcined to soda ash or from trona ore calcined to impure soda ash and then purified. Sodium carbonate is also synthesized from limestone by the Solvay process.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used in food as an antioxidant as defined in § 170.3(o)(3) of this chapter, curing and pickling agent as defined in § 170.3(o)(5) of this chapter, flavoring agent and adjuvant as defined in § 170.3(o)(12) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, and processing aid as defined in § 170.3(o)(24) of this chapter.

(d) The ingredient is used in food, in accordance with § 184.1(b)(1), at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.1 percent in baked goods as defined in § 170.3(n)(1) of this chapter, 0.04 percent in nonalcoholic beverages as defined in § 170.3(n)(3) of this chapter, 0.4 percent in confections and frostings as defined in § 170.3(n)(9) of this chapter, 0.2 percent in gelatins, puddings, and fillings as defined in § 170.3(n)(22) of this chapter, 0.1 percent in processed vegetables and vegetable juices as defined in § 170.3(n)(36) of this chapter, 0.3 percent in sweet sauces, toppings, and syrups as defined in § 170.3(n)(43) of this chapter, and 0.05 percent or less in all other food categories.

§ 184.1792 Sodium sesquicarbonate.

(a) Sodium sesquicarbonate ($Na_2CO_3 \cdot NaHCO_3 \cdot 2H_2O$, CAS Reg. No. 533-96-0) is prepared by partial carbonation of soda ash solution followed by crystallization, centrifugation, and drying.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used as a pH control agent as defined in § 170.3(o)(23) of this chapter.

(d) The ingredient is used in cream, in accordance with § 184.1(b)(1), at levels not to exceed good manufacturing practice. Current good manufacturing practice utilizes a level of the ingredient sufficient to control lactic acid prior to pasteurization and churning of cream into butter.

PART 186—INDIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

5. In Part 186 by adding new §§ 186.1736 and 186.1742 to read as follows:

§ 186.1736 Sodium bicarbonate.

(a) Sodium bicarbonate ($NaHCO_3$, CAS Reg. No. 144-55-8) is prepared by dissolving sodium carbonate and treating the solution with carbon dioxide. As carbon dioxide is absorbed, a suspension of sodium bicarbonate forms. The slurry is filtered, forming a cake which is washed and dried.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used as a constituent of cotton and cotton fabrics used in dry food packaging materials.

(d) The ingredient is used at levels not to exceed good manufacturing practice.

§ 186.1742 Sodium carbonate.

(a) Sodium carbonate (Na_2CO_3, CAS Reg. No. 497-19-8) is derived either from purified trona ore that has been calcined to soda ash or from trona ore calcined to impure soda ash and then purified. Sodium carbonate is also synthesized from limestone by the Solvay process.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used as a constituent of food-packaging materials.

(d) The ingredient is used at levels not to exceed good manufacturing practice.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of these ingredients in food under conditions different from those proposed herein or different from that in Part 181. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulation proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act (21 U.S.C. 342), and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time. This notice also constitutes a proposal to establish a regulation under Part 181, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before August 14, 1978, submit to the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this proposal will not have a major economic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107.

Dated: May 17, 1978.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Regulatory Affairs.

NOTE.—Incorporation by reference was approved by the Director of the Office of the Federal Register on July 10, 1973, and is on file in the Federal Register Library.

[FR Doc. 16253 Filed 6-12-78; 8:45 am]

[4110-03]

[21 CFR Parts 314, 429 and 431]

[Docket No. 78N-0127]

DEFINITION OF "UNITED STATES"

Withdrawal of Proposal and Termination of Rulemaking Proceeding

AGENCY: Food and Drug Administration.

ACTION: Withdrawal of proposal.

SUMMARY: The Commissioner of Food and Drugs is withdrawing a proposal to define the term "United States" for establishing residency requirements or place of business requirements for authorized agents of foreign new drug applicants or manufacturers. Upon further consideration of the proposal, the Commissioner has concluded that rulemaking in this matter is not necessary.

EFFECTIVE DATE: June 13, 1978.

FOR FURTHER INFORMATION CONTACT:

Philip L. Paquin, Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-7220.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of July 18, 1973 (38 FR 19130), the Commissioner issued a proposal to define the term "United States." The proposed rule would have amended §§ 310.3 and 429.40 (21 CFR 310.3 and 429.40) (formerly 21 CFR 130.1 and 164.2 respectively, both of which were recodified

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